# REMARKS

## I. Status of Claims

Currently, claims 1-10, 12-18, 21-29, and 31-46 are pending in this application. Claims 12, 14, 16-18, 21-24, and 31-39 have been withdrawn from consideration by the Office as directed to non-elected inventions. In the Request for Continued Examination filed concurrently with this Amendment, Applicant has requested that the Office enter the Amendment After Final dated 17 October 2007.

In addition, by this Amendment, Applicant adds claims 42-46, which depend from claims 1, 3, 5, 7, and 9 and recite that the high pH ranges from 9.5 to 12. Support for this amendment can be found throughout the specification, including, for example, at page 12, lines 17-20, page 29, lines 4-8, Figure 2, and page 80-82. 11, lines 3-24. Accordingly, the amendment does not introduce any new matter.

## II. Objection to the Specification

The Office maintained the objection to the specification asserting that "the trademark DEEP VENT® needs to be capitalized." Final Office Action at 2. Applicant respectfully traverses this objection.

As noted in the M.P.E.P., "the use of trademarks having definite meanings is permissible in patent applications . . . . Trademarks should be identified by capitalizing each letter of the mark (in the case of word or letter marks) *or otherwise indicating the description of the mark (in the case of marks in the form of a symbol or device or other nontextual form*). M.P.E.P.

§608.01(v) (emphasis added). Applicant respectfully submits that the Deep $Vent_R$™ (exo-) (New England BioLabs) trademark used in this application has a fixed and definite meaning in the art. Previously, the specification was amended by either capitalizing each letter of each trademark (e.g., VENT) or by using the appropriate symbol to indicate a trademark (i.e., Deep $Vent_R$™). Accordingly, Applicant respectfully requests the Office to withdraw this objection.

## III. Rejection Under 35 U.S.C. §112, First Paragraph

The Office rejects claims 1-11, 13, 15, 19, and 25-30 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not enable one of skill in the art to make and use the invention commensurate in scope with the claimed invention. Final Office Action at 5. In the Final Office Action, the Office acknowledges that the specification enables the claimed subject matter for a range of pH from 9.3 to 10, but asserts that it "does not reasonably provide enablement for a range of pH 9.3 to 14." *Id.*

In response to Applicant's arguments set forth in the 17 October 2007 Amendment After Final, the Office now acknowledges that the application enables a pH range of 9.5 to 12 but continues to assert that it "does not enable the claimed range of 9.3 to 14." Advisory Action at 2. As an initial matter, Applicant notes that this rejection does not apply to new claims 42-46, which recite that the pH range is 9.5 to 12. Applicants respectfully traverse this rejection as to the remaining claims.

An Applicant's specification is ***presumptively enabled*** for the full scope of the claims. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971) (emphasis added); *accord*, M.P.E.P. §

2164.04. In fact, "[a]s a matter of Patent Office practice . . . [a specification] must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements." *In re Armbruster*, 185 USPQ 152, 153 (C.C.P.A. 1975).

The M.P.E.P. specifically states that the Office has the initial burden to establish a reasonable basis to question the enablement of the claimed invention. M.P.E.P. § 2164.04. This reasonable basis may be established by the Office by "making specific findings of fact, supported by evidence, and then drawing conclusions based on these findings of fact". . . "[h]owever, specific technical reasons are always required." *Id.* Absent such evidence, the burden does not shift to the Applicant. *In re Marzocchi*, 169 USPQ at 369.

Here, the specification discloses that the fusion DNA polymerases and fusion DNA polymerase blends of the invention will work at a high pH (*i.e.*, 9.1 to 14). Specification at page 26, lines 17-23; see also, page 12, lines 17-20. The Office provides no reasonable basis to doubt the objective truth of the statements in the specification. The only arguments set forth by the Office to date rest on faulty presumptions and have been addressed in Applicant's Amendment After Final filed 17 October 2007.

First, the Office asserted that the specification does not disclose that the DNA fusion polymerase will operate above pH 10. As noted previously, however, the specification provides working examples showing that Pfu-Sso7d fusions and polymerase blends comprising the same efficiently amplify DNA in reaction buffers with a pH ranging from 9.5 to 12. Second, the

Office attempts to rely on U.S. Patent No. 4,545,933 ("the '933 patent") to argue that the "quantity of experimentation in this area is extremely large since there the art teaches that protein hydrolyses at pH 10 and higher." Final Office Action at 5. As demonstrated by the working examples of this application, however, Applicant's fusion DNA polymerases operate efficiently at a pH well above 10. Therefore, the specific teaching about the hydrolysis of casein proteins in the '933 patent does not extend to the fusion DNA polymerases recited in the pending claims. Moreover, given the working examples in the current specification showing that Applicant's fusion DNA polymerases operate efficiently between pH 9.5 and 12, one of skill in the art would have no reason to think that the fusion DNA polymerases would not work at a pH higher than 12. Accordingly, the Office has not met its initial burden to establish a reasonable basis to question the enablement for the claimed pH range of 9.3 to 14. M.P.E.P. § 2164.04. Therefore, Applicant respectfully requests that the Office reconsider and withdraw this enablement rejection of claims 1-11, 13, 15, 19, and 25-30.

## IV. Rejections Under 35 U.S.C. § 103

### A. *Wang* Does Not Render Claims 1-4, 7-11, 13, 15, 19, 25-30, and 40 Obvious

The Office rejects claims 1-4, 7-11, 13, 15, 19, 25-30, and 40 under 35 U.S.C. § 103(a) as allegedly obvious over WO 01/082501 (*Wang*). Final Office Action at 6. Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2143. Applicant

submits that *Wang*, alone, or in combination with the state of the art, does not teach all of the elements of the rejected claims. As acknowledged by the Office, "Wang does teach pH 8.8 but does not specifically teach the pH range of 9.3 to 10." *Id.* at 9. The Office asserts "it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention was made to use a pH in [*sic*, the] range of 9.3-10 as used by the applicant which is in the range of pH 8.8 as used by Wang, since these differences in pH would not be expected to greatly alter the conditions for amplification." *Id.* Applicant respectfully disagrees.

One of the factual inquiries underlying the obviousness standard set forth in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), is the level of ordinary skill in the art. *See* M.P.E.P. §2141. As part of this response, Applicant submits a Declaration Under 37 C.F.R. § 1.132 of the inventor, Michael Borns ("Declaration"). Applicant submits that one of ordinary skill in the art would have had at least an undergraduate degree in a relevant art, such as molecular biology or biochemistry, coupled with relevant laboratory experience using DNA polymerases. Accordingly, as of at least the 25 March 2003 filing date of the priority application (Provisional Application No. 60/457,426), the Declarant, Michael Borns, qualifies as a person of ordinary skill in the art. *See* Declaration at ¶ 4.

*Wang* discloses the standard reaction buffer for wild type Pfu polymerase, which contains 20 mM Tris-HCl (pH 8.8) as a buffering component. *Wang* similarly discloses the use of the same buffer with an additional 40 mM of KCl for Taq polymerase, a Pfu-Sso7d polymerase fusion, and an Sso7d-Taq polymerase fusion. This is consistent with the specification, which

notes that the buffering component in standard PCR reaction buffers ranges from 8.3 – 8.8. *See* Specification at page 26, lines 21-23 and page 63, lines 20-21; *see also* Declaration at ¶ 7.

First, Applicant notes that if the buffering component in the standard PCR reaction ranges from 8.3 to 8.8, once the buffering component is added to the PCR reaction buffer, the final pH of the PCR reaction buffer will be slightly lower than the pH of the buffering component. *See* Declaration at ¶ 8. Second, and more significantly, one of ordinary skill in the art having experience working with DNA polymerases would expect that using a wild type Pfu DNA polymerase, or another wild type DNA polymerase, in a reaction buffer having a pH above 9 would impair PCR performance. *See* Declaration at ¶¶ 9-10. As the pH increases above 9, one of ordinary skill in the art would expect an inverse relationship with the PCR performance of standard DNA polymerases, such as Pfu. *See* Declaration at ¶ 9. A recently performed experiment confirms this.

Specifically, Attachment B of the Declaration shows that wild type Pfu polymerase efficiently amplifies target DNA in a reaction buffer ranging from pH 8.3 to 8.8. *See* Declaration at ¶¶ 11-13. However, when the pH was increased above 9, the efficiency of the Pfu amplification activity dropped dramatically. *See* Declaration at ¶ 13. The results in Attachment B are consistent with what one of ordinary skill in the art would have expected as of 25 March 2003. *See* Declaration at ¶ 13.

Thus, one of ordinary skill in the art would not be motivated to increase the pH of the reaction buffer disclosed in Example 6.1 of Wang to a pH of 9.3 or higher because he would

expect that such a change would significantly impair the conditions for amplification with either the wild type Pfu DNA polymerase or the Pfu-Sso7d fusion polymerase. *See* Declaration at ¶ 16. Accordingly, contrary to the Office's assertions, and absent the teachings of the present specification, one of ordinary skill in the art having experience working with DNA polymerases would expect the differences between the conventional pH used for Pfu-based PCR in Wang (about 8.3 to 8.8) and the pH recited in the pending claims (9.3 to 14) to significantly impair the efficiency of PCR performance. *See* Declaration at ¶ 16.

Also, it appears that in Example 6.1, Wang used a commercially available reaction buffer for Pfu. *See* Declaration at ¶ 15. One of ordinary skill in the art would not have been motivated to increase the pH of this reaction buffer as a matter of routine optimization for the additional reason that, as a commercial product, the reaction buffer would have already been optimized. *See* Declaration at ¶ 16.

Furthermore, Applicant has unexpectedly discovered that high pH enhances the amplification efficiency of Applicant's fusion DNA polymerases and blends comprising the same as shown, for example, by decreased extension times in PCR reactions. *See* Declaration at ¶ 18. For example, as disclosed in the specification, the more processive Pfu-Sso7d fusion polymerase was able to amplify a 6kb human beta globin genomic target sequence with an extension time of 15 seconds per kb at high pH, whereas "*Pfu* Turbo [*i.e.*, wild type Pfu] alone cannot amplify this target at 15 seconds per kb." *See* Specification, page 80, lines 3-9. "Amplification [of the 6kb human beta globin genomic target] appears at pH 8.5 and is strongest

between pH 10-12, demonstrating the enhancing effect of high pH on the chimeric *Pfu*-Sso7d DNA polymerase (figures 1 & 2)." *Id.* at page 80, lines 9-10. In addition, Applicant demonstrated the superiority of his high pH buffers as compared with the state of the art Pfu buffer of *Wang*. More specifically, PCR amplifications using a blend comprising a Pfu-Sso7d fusion and pH 10 and 11.8 reaction buffers "were dramatically superior to the 1.5X cloned *Pfu* buffer, further demonstrating the enhancing effects of high pH for PCR amplification with *Pfu*-Sso7d (figure 3)." Specification at page 80, line 12 to page 81, line 2. These results also directly contradict the state of the art that teaches increasing the pH above 9 with standard polymerases, such as Pfu, reduces the efficiency of the PCR performance. *See* Declaration at ¶ 9.

Accordingly, Applicant submits that *Wang*, alone, or in combination with the state of the art, fails to teach or suggest all elements of claims 1-4, 7-11, 13, 15, 19, 25-30, and 40 and, thus, does not render those claims obvious. For at least this reason, Applicant requests that the Office reconsider and withdraw the rejection of claims 1-4, 7-11, 13, 15, 19, 25-30, and 40 as unpatentable over *Wang*.

### B. *Wang* in Combination with *Sanger* Does Not Render Claims 5 and 6 Obvious

The Office rejects claims 5 and 6 under 35 U.S.C. § 103(a) as allegedly obvious over *Wang* in combination with *Sanger*. Office Action at 11. Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2142. Applicant

submits that the combined teachings of the cited references do not teach all of the elements of the rejected claims. For the reasons discussed above, *Wang* fails to teach or suggest a pH from 9.3 to 14. *Sanger* also fails to teach or suggest this element of the claims and thus fails to remedy the deficiencies of *Wang*.

Accordingly, Applicant submits that the combined teachings of *Wang* and *Sanger* fail to teach or suggest all elements of claims 5 and 6 and, thus, do not render those claims obvious. For at least this reason, Applicant requests that the Office reconsider and withdraw the rejection of claims 5 and 6 as unpatentable over the combination of these references.

## V. Conclusion

Applicant believes that all of the substantive issues raised in the Final Office Action mailed 17 August 2007 have been addressed, and all objections and rejections overcome. Accordingly, Applicant believes that this application is in condition for allowance. If the Office believes anything further is required in order to place this application in even better condition for allowance, Applicant requests that his undersigned representative be contacted at the number listed below to discuss remaining issues.

Please grant any extensions of time required to enter this paper and charge any additional required fees to Deposit Account No. 50-3740.

Respectfully submitted,
Michael BORNS

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Attachment:

Declaration Under 37 C.F.R. §1.132